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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/444,284	VOGELS ET AL.	
	Examiner	Art Unit	
	Christopher Drabik	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-21,26,28-32 and 37-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-21,26,28-32 and 37-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☐ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other: .

Detailed Action

Minor Informalities

Claim 26 is objected to because of the following informalities: Claim 26 would set forth the claimed subject matter more clearly if the phrase "...administering to said cells an adenovirus capsid comprises proteins..." was changed to "...administering to said cells an adenovirus capsid **comprising** proteins..."

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1, 4-11, 13-18, 21 and 43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 sets forth the grouping "smooth muscle cells, endothelial cells, or smooth muscle cells and epothelial (sic) cells." The word "epothelial" appears to be a misspelling. This renders the claim unclear and it is not readily apparent what the applicants specifically mean to claim epithelial or endothelial cells. Claims 3-11, 13-18, 21 and 43 depend from claim 1 and, hence are bound to the limitations of claim 1.

Claim 2 , 38-40 and 42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 2 recites: "A gene delivery vehicle

having been **deprived** of at least a tissue tropism for liver cells." The claim is unclear because it is not apparent what the applicants mean by deprived. In example 2, applicants provide the biodistribution of several gene delivery vehicles all of which appear to transduce liver cells. Claims 38-40 and 42 depend from claim 1 and, hence, are bound to the limitations of claim 1.

Claims 10, 15 and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "derived" renders the claims indefinite because the term merely indicates a source. The final product may have gone through any number of derivations such that it is not clear as to what applicants intend to claim.

Claim 12 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 12 is deficient in reciting the claim number on which it depends.

Claim 29-31are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 29-32 recite sequences from adenovirus 5 as limitations of the claimed plasmids. The genome of adenovirus 5 has at least 2 known

GENbank accession numbers each file having a different total number of nucleotides. See e.g. accession number NC_001406 which gives the genome size as being 35935 nucleotides in length. Claim 30 seems to indicate the size of the genome is at least 35938 nucleotides in length. This points to a discrepancy in the field regarding the exact sequence of Ad-5. This discrepancy makes the limitations of the claim indefinite.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 2, 25, 37-40 and 42 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claims 2 and 25 are drawn to a gene delivery vehicle which has been deprived or is lacking a tissue tropism for liver cells. Cl Claim 37 is drawn to a method of depriving an adenovirus capsid of liver cell binding tropism wherein the capsid comprises fiber protein from adenovirus 16, Claims 38 –40 and 42 are drawn to gene delivery vehicles wherein said tropism is provided by the capsid, said capsid can comprise protein fragments from at least two different viruses, wherein at least one of said viral protein fragments is from adenovirus, and wherein at least one of said viral protein fragments is from an adenovirus of subgroup b.

Based on claim 2, the scope of the invention encompassed by claims 2 and 37-40 reads on any vehicle used for introducing a foreign gene into cells either *in vitro or in vivo* with the proviso that the vehicle is not capable of transducing liver cells. The nature of the invention has to do with the construction of a chimeric viral capsid employing fiber protein fragments from adenovirus subgroup b, or specifically of adenovirus 16, in conjunction with capsid proteins and other constituent genes of adenovirus 5. This construction, it is claimed , has the ability to avoid gene delivery to the liver.

While the language of claims 2 and 37 expressly claims a gene delivery vehicle ***deprived*** of a tissue tropism for liver, the data provided by the applicants in example 2 seems to contradict this assertion. In this example, applicants injected the capsid constructs into the tail vein of mice and subsequently measured the expression of a reporter gene in cell lysates of harvested tissues. The applicants measure reporter luciferase activity in liver, spleen, lung, kidney, heart and brain cell lysates. For the subgroup B chimeric capsid, based on Ad-16 fiber protein fragment, the expression in liver cells appears to be higher than in all other tissues tested. Indeed, table II seems to indicate that the efficiency of transduction is roughly 20 – 40 fold ***more*** efficient in transducing liver cells than other tissues. The biodistribution is markedly different from that of the Ad-5 construct, however, the invention claims gene delivery vehicles which do not transduce liver cells. This is clearly not demonstrated.

While it may be argued that the reduced liver expression in the Ad-16 chimera infected mice relative to the Ad-5 infected mice suggest a ***reduced*** tropism for liver cells, this may also simply reflect the viruses poor overall ability to infect all types of

cells tested in this example: The experiment used equal amounts of viral particles, Ad-5 or Ad-16 chimera, to infect mice, yet the total amount of transgene activity from all cell types tested is significantly lower in the mice infected with the Ad-16 chimera. In the absence of data indicating the fate of the majority of Ad-16 chimera virus it is difficult to conclude that a tropism for cells other than liver cell is indicated. In any event, the data as disclosed does not support the assertion that the Ad-16 capsid construct is deprived of the ability to deliver a gene to liver cells.

Based on the breadth and unclear assertions of the claims and the seemingly contradictory data provided in example 2 it is not apparent that one skilled in the art could make or use the invention commensurate with the claims and hence claims 2, 37-40 and 42 is appropriately rejected as not meeting the patentability requirements of 35 USC 112, paragraph 2

Claim 15 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claim 15 is drawn to a gene delivery vehicle derived from an adenovirus and is modified such that a host organism's immune response to said gene delivery vehicle is reduced or disabled. The nature of the invention has to do with an encapsidated adenoviral nucleic acid vector comprising adenoviral capsid proteins, said capsid proteins can comprise fragments from several different adenovirus

subtypes. Significantly, constructs of this type putatively have the ability to avoid or reduce host immune response.

Applicants disclose several means by which an adenoviral vector might be constructed such that an immune response may be avoided. Applicants suggest choosing capsid proteins which have a reduced immunogenicity (page 15, lines 26-30) or by deleting adenovirus 5 genes in early region 2, 3 or 4 (page 26, lines 21-32). The applicants do not provide specific guidance in generating such constructs and no examples of gene delivery vehicles having reduced immunogenicity are disclosed.

Immune responses to adenoviral vectors pose a considerable problem for the long term expression of transgenes. Verma et al in reviewing the difficulties of adenoviral gene transfer write "...the immune system is behind the short term [transgene] expression that is usually obtained from adenoviral vectors...The immune reaction is potent eliciting both the cell-killing 'cellular ' response and the antibody-producing 'humoral' response. " (Verma et al (1997)Nature 389: 239-242, see columns 1 and 2, page 241.) Indeed, it is well established in the art that adenoviruses elicit strong humoral and cellular immune responses. This is a significant hurdle to overcome, because attempts to achieve longer term expression generally involve repeat administration of recombinant adenoviral vector. Second administrations of virus generally elicit increased immune responses leading to very inefficient gene transfer. Hence Wilson et al state "Most often the second administration of adenoviral vector is inefficient or impossible because of the cellular and humoral immune responses that mimic the immune response to any viral infection" (Wilson et al (1999) Adenovirus

Vectors in *The Development of Gene Therapy*, Friedman, T ed. CSHL Press, Cold Spring Harbor, New York. see page 86). Verma et al conclude by stating "There are considerable immunological problems to be overcome before adenoviral vectors can be used to deliver genes and produce sustained expression." (p 241, second column)

Applicants suggest that the selective deletion of adenoviral genes is a means for circumventing immune response, however, this approach appears to be incompletely predictable. For example, Lusky et al, in experiments directed to understanding the influence of host immune response to viral antigens on the in vivo persistence of transduced cells, generated a set of vectors with single deletions (AdE1) or double deletions (AdE1/E2A and AdE1/E4) and observed the vectors immunogenicities in vivo. (Lusky et al (1998) Journal of Virology, 72:2022-2032 see abstract and page 2023, second paragraph). A principal conclusion from these experiments was that "...the progressive deletion of the adenovirus genome does not extend the in vivo persistence of the transduced cells and does not reduce the antivirus immune response." (see abstract). Therefore, applicants assertion that deleting adenoviral genes in the early 2 or 4 regions does not appear to be a straightforward means for avoiding host organism immune response and, at least, significant supplemental experimentation would be required to practice the invention as claimed.

In regards to reducing immunogenicity of gene delivery vehicles based on capsid protein selection, applicants point to the selection of capsid proteins, which include hexon, penton and fiber proteins, from adenoviruses that show reduced immunogenicity in host organisms. The capsid proteins are to be determined

functionally by a hosts reduced immune response. Despite the fact that there are 41 known adenovirus subtypes, applicants do not state specifically which adenoviral hexons or pentons or combinations thereof they deem functional in their gene delivery system. Fiber protein switching, however, does not in all cases seem to yield results which reduce host immune response. For example, Gall et al disclose experiments in which chimeric Ad5/Ad7 capsids were generated. (Gall et al (1996) Journal of Virology, 70:2116-2123) In there experiments they show that neutralizing antibodies developed to the same extent against Ad-5 vectors expressing Ad-5 fiber or Ad 5 vectors altered to express Ad-7 fibers. (see abstract and table 1, page 2122). It is significant to note that Ad-7 is from the same subgroup as Ad-16, hence the capsid constructs of Gall et all encompass claims in the instant application to subgroup b fiber-containing gene delivery vehicles

Considering the nature of the invention, the state of the art, the amount of direction provided, the lack of working examples and the quantity of experimentation required it is not apparent that one of skill in the art would be enabled to predictably modify adenoviral gene delivery vehicles such that a host immune response has been reduced or disabled.

Claim 29-31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. As stated above, claims 29-31 recite adenovirus

sequences without providing adequate sequence information regarding the genome of the adenovirus claimed. This rejection may be obviated by appropriate deposit of the nucleic acid constructs claimed.

If a strain(s) is not so obtainable or available, the requirements of 35 USC 112 may be satisfied by deposit thereof. The specification does not disclose a repeatable process to obtain the exact same strain(s) and it is not apparent that if such strain(s) are readily available to the public. If the deposit of the virus strain(s) is made under the terms of the Budapest Treaty, then an affidavit or declaration by the applicants, or a statement by an attorney of record over his or her signature and registration number, stating that the strain(s) of will be irrevocably and without restriction or condition released to the public upon issuance of a patent would satisfy the deposit requirements herein.

If the deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.801 – 1.809, applicants may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number showing that

(a) during the pendency of the application, access to the invention will be afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer;

(d) the viability of the biological material at the time of deposit will be tested (see 37 CFR 1.807); and

(e) the deposit will be replaced if it should ever become inviable

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 4-8, 10-14, 16, 17, 19, 24, 26, and 41 are rejected under 35 U.S.C. 102(b) as being anticipated by Stevenson et al. (Stevenson et al (1997) Journal of Virology 71: 4782-4790)

Claims 1, 4-8, 10-14, 16, 17, 19, 24, 26, and 41 are drawn to a gene delivery vehicle comprising a tropism for smooth muscle cells, endothelial cells, or smooth muscle cells and epothelial (sic) cells, wherein said tropism is provided by a virus capsid , said virus capsid comprises protein fragments from two different viruses, said protein fragments can be from adenovirus or adenovirus subgroup b, wherein said tissue tropism is provided by said protein fragments which comprise the fiber protein of adenovirus subgroup b, said gene delivery vehicle also comprises nucleic acids derived from an adenovirus or at least two adenoviruses, wherein said nucleic acid encodes a fiber protein comprising at least a tissue tropism determining fragment of adenovirus subgroup b, said adenovirus derived nucleic acid is modified such that replication of virus is at least reduced, said nucleic acid also comprises non-adenoviral nucleic acid, a

method of delivering nucleic acid to cells, and a cell line for producing a gene delivery vehicle.

Stevenson et al disclose an adenovirus that has the ability to infect human venous endothelial cells (see page 4788, figure 6), hence the recitation of claim 1 regarding a gene delivery vehicle having a tropism for endothelial cells is clearly anticipated. The construct of Stevenson et al comprises capsid proteins from at least two adenoviruses which impart the viruses ability to bind to endothelial cells. At least one of said capsid proteins comprises fragments from adenovirus 3, a subgroup b adenovirus, therefore the limitations of claims 4-7 are clearly anticipated by the disclosure of Stevenson et al. (see page 4783 Materials and Methods section, see also page 4784, figure 1) Furthermore, the capsid protein comprises the fiber protein of adenovirus 3, clearly anticipating claim 8.

The recombinant adenovirus described by Stevenson et al comprises a chimeric fiber protein in which the Ad5 tail and shaft domain were fused to the Ad3 head region. Ad 5 is a subgroup c adenovirus. This chimeric protein was encoded in a nucleic acid vector which also encoded Ad5 proteins sufficient to direct the construction of chimeric capsids in a human kidney derived cell line. Protein and protein fragments of the recombinant adenovirus not from Ad3 (subgroup b) are disclosed as being from Ad5 (subgroup c) which meets the limitation of claim 10(see page 4783). Furthermore, the adenovirus described by Stevenson et al contains nucleic acid sequence encoding the chimeric Ad3/Ad5 capsid, meeting the nucleic acid limitations of 12 and 13. The adenoviral nucleic acid of Stevenson et al lacks an E1 gene which inherently reduces the

vectors ability to replicate anticipating the limitation of a replication-reduced gene delivery vehicle in claim 14. In addition, the adenovirus contained nucleic acid encoding a reporter gene (β–gal) which meets the limitation of claim 17 reciting that the gene delivery vehicle comprise non-adenoviral nucleic acid.

The adenoviral vector disclosed in Stevenson et al comprises an adenoviral genome in which E1 and E3 has been deleted, anticipating the minimal adenovirus vector of claim 16. Claim 19 recites a cell for the production of a gene delivery vector having a tissue tropism, said gene delivery vehicle comprising an adenoviral subgroup b tissue tropism determining fiber protein fragment. Stevenson et al discloses a human kidney derived cell line producing a recombinant adenovirus comprising a tropism for endothelial cells and also comprising a capsid containing subgroup b fiber protein tropism determining fragment. Therefore, the limitations of claim 19 are clearly anticipated by Stevenson et al.

The adenoviral vector disclosed in Stevenson et al comprises an adenoviral capsid having the ability to infect endothelial cells, comprises proteins from Ad-5 and Ad-3, and comprises a tissue tropism determining fragment from a subgroup b adenovirus (Ad-3), therefore the limitations of claim 24 and 41 are clearly anticipated.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 18 rejected under 35 U.S.C. 103(a) as being unpatentable over Stevenson et al. (Stevenson et al (1997) Journal of Virology 71: 4782-4790).

Stevenson et al teaches a gene delivery vehicle which has the capability of transducing endothelial cells. The construct of Stevenson et al comprises components of adenoviral and non-adenoviral DNA. The construct further comprises a foreign gene (CAT) and it is clearly demonstrated that the vector is capable of mediating the expression of a foreign in endothelial cells.

Claim 18 is drawn to a gene delivery vehicle which can transduce endothelial cells or smooth muscle cells and consists of non-adenoviral nucleic acids chosen from a group of genes coding for a protein, said group consists of apolipoprotein, a nitric oxide synthase, a herpes simplex thymidine kinase, an interleukin-3, an interleukin1α an (anti) angiogenesis protein, an anti proliferation protein, a smooth muscle cell anti-migration protein, a vascular endothelial growth factor, a basic fibroblast growth factor, a hypoxia inducible factor and PAI-1.

The use of vectors for the transduction of cells is commonly practiced in the art. Further, a commonly acknowledged goal of the art is the expression of a desired gene based on the transduction of cells. The group of genes claimed by the applicants have

obvious applications in the art of cell and molecular biology. As an example, the use of thymidine kinase as a suicide gene for gene therapy approaches has been used by Guzman et al. (Guzman et al (1994) PNAS 91: 10733-10736). It should be noted that Guzman et al use a gene delivery vehicle for the transduction of endothelial cells using methods comprising a number of the essential elements encompassed by claim 18, further providing evidence that the methods of gene delivery and gene delivery vehicles of claim18 have been applied previously. Given Stevenson et al has shown that a vector consisting of the elements of claim 18 can be used to cause the expression of a desired gene in a cell, it would have been prima facie obvious to one of skill in the art to combine the gene delivery vehicle of Stevenson et al with other desired genes.

Conclusion

No claim set forth in the instant application is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher Drabik whose telephone number is 703-605-1156. The examiner can normally be reached on Monday-Friday from 9am to 5pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Clark, can be reached on 703- 305-4051. The fax phone number for the organization where this application or proceeding is assigned is 703-308-4242.

Inquiries of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-

1234. Questions regarding review of formality issues may be directed to Kim Davis, the patent analyst assisting in this application. She may be reached at 703-305-3015.

Christopher E. Drabik
April 9, 2001

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